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Hypoxia and matrix viscoelasticity sequentially regulate endothelial progenitor cluster-based vasculogenesis

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Abstract:

Vascular morphogenesis is the formation of endothelial lumenized networks. Cluster-based vasculogenesis of endothelial progenitor cells (EPCs) has been observed in animal models, but the underlying mechanism is unknown. Here, using O_2-controllable hydrogels, we unveil the mechanism by which hypoxia, co-jointly with matrix viscoelasticity, induces EPC vasculogenesis. When EPCs are subjected to a 3D hypoxic gradient ranging from < 2 to 5 %, they rapidly produce reactive oxygen species that up-regulate proteases, most notably MMP-1, which degrade the surrounding extracellular matrix. EPC clusters form and expand as the matrix degrades. Cell-cell interactions, including those mediated by VE-cadherin, integrin-β2, and ICAM-1, stabilize the clusters. Subsequently, EPC sprouting into the stiffer, intact matrix leads to vascular network formation. In vivo examination further corroborated hypoxia-driven clustering of EPCs. Overall, this is the first description of how hypoxia mediates cluster-based vasculogenesis, advancing our understanding toward regulating vascular development as well as postnatal vasculogenesis in regeneration and tumorigenesis.

Keywords: vasculogenesis, endothelial progenitor cells, hydrogel, hypoxia, MMP-1 protease, cell-cell interaction